hydro-5-ethyl-2H-azepin-2-one, 126694-36-8; (R)-hexahydro-5-(1,1-dimethylethyl)-2H-azepin-2-one, 126872-02-4; (4R,6S)-hexahydro-4,6-dimethyl-2H-azepin-2-one, 126785-73-7; (R)-hexahydro-5-methyl-5-phenyl-2H-azepin-2-one, 126694-37-9; (R)-hexahydro-5-hydroxy-2H-azepin-2-one, 126694-38-0.

Supplementary Material Available: Experimental details of crystal data, intensity measurements, and structure solution and refinement, tables of fractional coordinates and equivalent isotropic thermal parameters, anisotropic thermal parameters, bond distances, bond angles, and torsion angles, and PLUTO representations of **11b** and **23a** (26 pages). Ordering information is given on any current masthead page.

Nonenzymatic Synthesis and Properties of 5-Aminoimidazole Ribonucleotide (AIR). Synthesis of Specifically ^{15}N-Labeled 5-Aminoimidazole Ribonucleoside (AIRs) Derivatives

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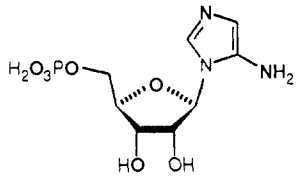
Abstract: The chemical synthesis of 5-aminoimidazole ribonucleoside (AIRs) and 5-aminoimidazole ribonucleotide (AIR) is described. The syntheses of specifically ^{15}N-labeled derivatives of AIRs are also described. These provide, by ^{15}N NMR determinations, unequivocal structure assignment of rearrangement products and of loci of protonation.

5-Amino-1-(β-D-ribofuranosyl)imidazole 5'-monophosphate, or 5-aminoimidazole ribonucleotide (AIR, **1**), is the precursor of the purine ribonucleotides in vivo[1] in both prokaryotic[2] and eukaryotic[3] systems. It is also the biosynthetic precursor of the pyrimidine portion of thiamin (vitamin B_1) in certain prokaryotic organisms.[4-7] Because of the pivotal role of AIR, it is a requisite for answering fundamental questions concerning these biosynthetic pathways, yet it has not been available in sufficient supply, well characterized,[8] to facilitate the examination of all of the biochemical and physicochemical properties that one would desire to investigate. Its availability until the present has depended upon phosphorylation of an enzymatically prepared precursor.[3,9-11] Moreover, the chemistry of AIR, the corresponding ribonucleoside (AIRs, **1a**), and related compounds[12] has been complicated by their often-mentioned lability during routine chromatographic purification procedures, concentration of solutions, or even dry storage at ambient temperature.[3,6,13]



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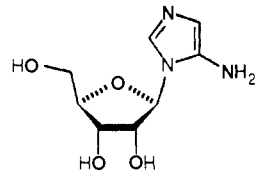
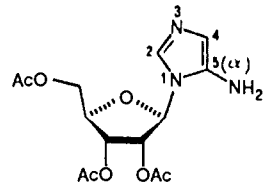


1a



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We have recently described a simple chemical (nonenzymatic) synthesis of 5-amino-1-(β-D-ribofuranosyl)imidazole (AIRs, **1a**),[14a] and further details are provided here. The compound 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICARs) was saponified in 6 M NaOH according to the method of Srivastava et al.[15,16] to yield sodium 5-amino-1-(β-D-ribofuranosyl)-imidazole-4-carboxylate (CAIRs, sodium salt). The strategem that permitted the isolation of pure AIRs was to release 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylic acid and effect its decarboxylation in a pH 4.8 aqueous NaOAc/HOAc buffer with N_2 bubbling through and *not* to use pH 7.0 conditions.

We were interested in extending the chemical synthesis of AIRs (**1a**) to 5-amino-1-(β-D-ribofuranosyl)imidazole 5'-phosphate (AIR, **1**)[3,9-11] so as to make this compound readily available in pure form and well characterized.[8] Compound **1a**, unprotected, was phosphorylated with pyrophosphoryl chloride in *m*-cresol[17] at 0 °C under argon to give 5-amino-1-(β-D-ribofuranosyl)-

† Fogarty Scholar-in-Residence, 1989-1990, National Institutes of Health, U.S. Public Health Service, Bethesda, MD 20892.

(1) See, for example: Stryer, L. *Biochemistry*, 3rd ed.; Freeman: New York, 1988; p 603.
(2) Schrimsher, J. L.; Schendel, F. J.; Stubbe, J.; Smith, J. M. *Biochemistry* **1986**, *25*, 4365.
(3) Schrimsher, J. L.; Schendel, F. J.; Stubbe, J. *Biochemistry* **1986**, *25*, 4356.
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(5) Estramareix, B.; David, S. *Biochem. Biophys. Acta* **1986**, *134*, 1136.
(6) Estramareix, B.; Thérisod, M. *J. Am. Chem. Soc.* **1984**, *106*, 3857.
(7) Yamada, K.; Kumaoka, H. *J. Nutr. Sci. Vitaminol.* **1983**, *29*, 389.
(8) Cf.: *The Merck Index*, 10th ed.; Windholz, M., Ed.; Merck & Co., Inc.: Rahway, NJ, 1983; p 29, "AIR. Isolated in soln only or as barium salt."
(9) Shaw, G.; Wilson, D. V. *J. Chem. Soc. C* **1962**, 2937.
(10) Cusack, N. J.; Shaw, G.; Litchfield, G. J. *J. Chem. Soc. C* **1971**, 1501.
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(15) Srivastava, P. C.; Mancuso, R. W.; Rousseau, R. J.; Robins, R. K. *J. Med. Chem.* **1974**, *17*, 1207.
(16) Srivastava, P. C.; Ivanovics, G. A.; Rousseau, R. J.; Robins, R. K. *J. Org. Chem.* **1975**, *40*, 2920.
(17) Imai, K.; Fujii, S.; Takonohashi, K.; Funikawa, Y.; Masuda, T.; Honjo, M. *J. Org. Chem.* **1969**, *34*, 1547.

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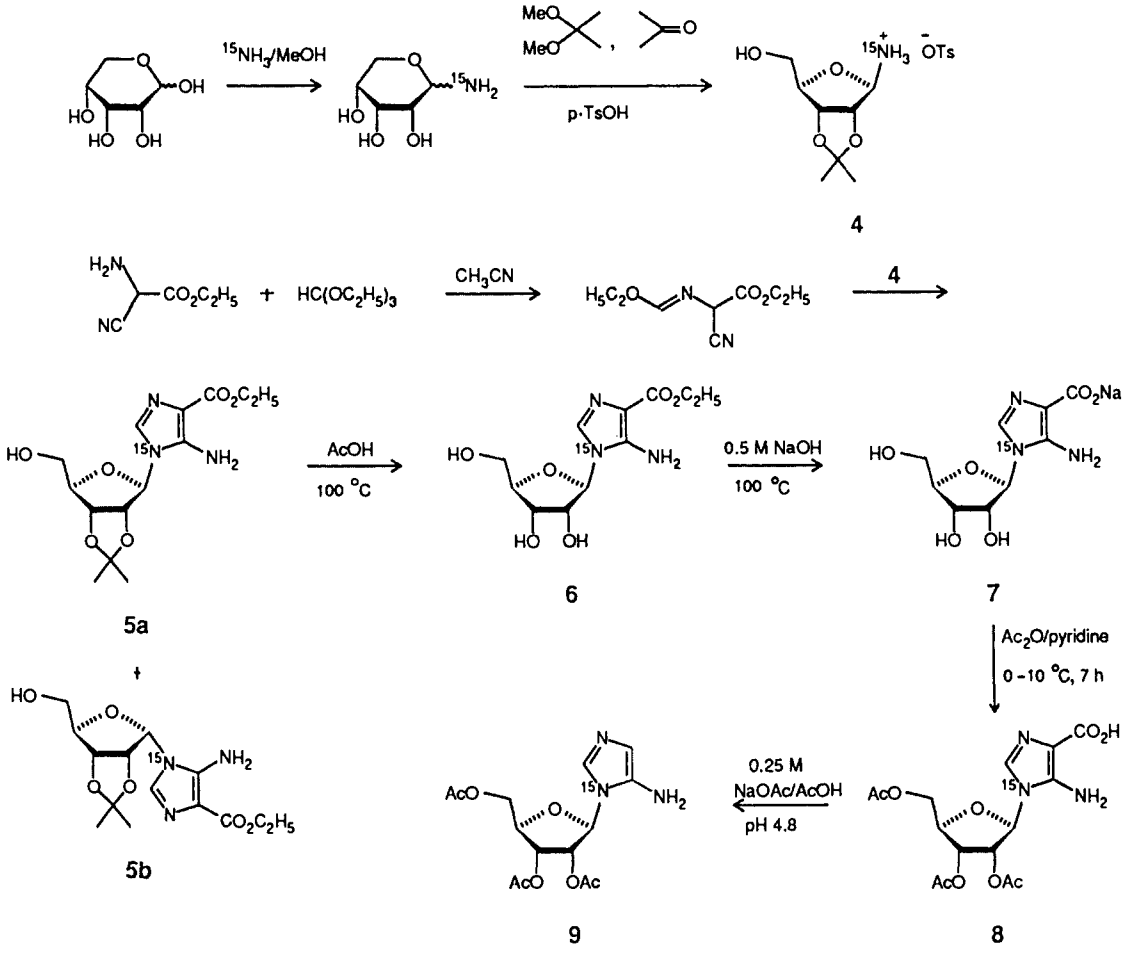
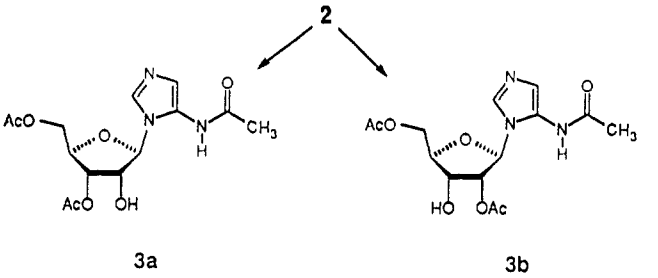
Scheme I



imidazole 5′-phosphate (**1**), which was isolated from a column of Sephadex A-25 ion exchanger resin, preequilibrated with triethylammonium bicarbonate (TEAB) buffer, by elution with a linear gradient of TEAB buffer. The monotriethylammonium salt of **1**, obtained as a gum, remained contaminated with TEAB in spite of our best efforts to remove the buffer by repeated coevaporation with 1:1 $MeOH/H_2O$ and drying in vacuo. However, it was found to be easy to effect exchange of the Et_3NH^+ salt to the NH_4^+ salt on a cation exchange resin, and the NH_4^+ salt was characterized by ^1H and ^{13}C NMR spectra and by low- and high-resolution mass spectra. This is one way to avoid contamination with TEAB. The H4 underwent very rapid exchange with D_2O as it did in the methanesulfonate salt of **1a**. The NH_4^+ salt was exchanged on a cation exchange resin for the Li^+ salt, a colorless hygroscopic solid that was also fully characterized spectroscopically. The ^1H and ^{13}C NMR signals observed for the NH_4^+ and Li^+ salts of AIR were much closer in position to those of AIRs methanesulfonate than to those of AIRs, suggesting that these salts are present in zwitterionic form, with protonation on N3 (see later).

The interesting behavior of the tri-*O*-acetyl derivative **2** of AIRs at neutral pH, communicated previously,[14a] has been examined in greater detail since we were apparently misled in our assumption of the formation of rearranged product α and β anomers in unequal proportion by the appearance of four NH signals in the natural abundance ^{15}N NMR.[14b] Further critical examination of the postulated rearrangement is germane to the hypothesis of an early biotic, bifurcated pathway to 9- and 3-substituted purine ribonucleotides.[18] We recognized that specific ^{15}N-labeling could differentiate among possible pathways for the rearrangement of **2**, determine the locus and measure the extent of protonation at separate nitrogens, and provide useful insight into the chemical behavior of AIR (**1**) and AIRs (**1a**). The reconsidered pathways for the rearrangment of **2** include the following: (A) migration of the 1-substituent to the exocyclic nitrogen (deribosidation, reribosidation), (B) Dimroth type rearrangement (ring opening and reclosure as in the case of the 1-alkyl-5-amino-1,2,3-triazoles),[19,20] or (C) *O*- to *N*-acetyl transfer (**2** → **3a**, **3b**).[21]



Accordingly, we have synthesized the three authentic 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazoles (**2**) labeled separately at the N1, N3, and $\alpha(NH_2)$ positions. The individual isomers were employed to determine sites of protonation and will no doubt find application in ongoing tracer experiments relating to biosynthesis. Facile rearrangement of **2** to a mixture of 5-acetamido-1-(3,5-di-*O*-acetyl-β-D-ribofuranosyl)imidazole (**3a**) and 5-acetamido-1-(2,5-di-*O*-acetyl-β-D-ribofuranosyl)-imidazole (**3b**) was confirmed by other chemical and spectroscopic means as well.

We relied upon the accumulated methodology of Shaw and his co-workers[9,22-26] for the synthesis of the specifically ^{15}N-labeled 5-aminoimidazole ribonucleoside derivatives. Any procedural

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(19) Albert, A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2659.
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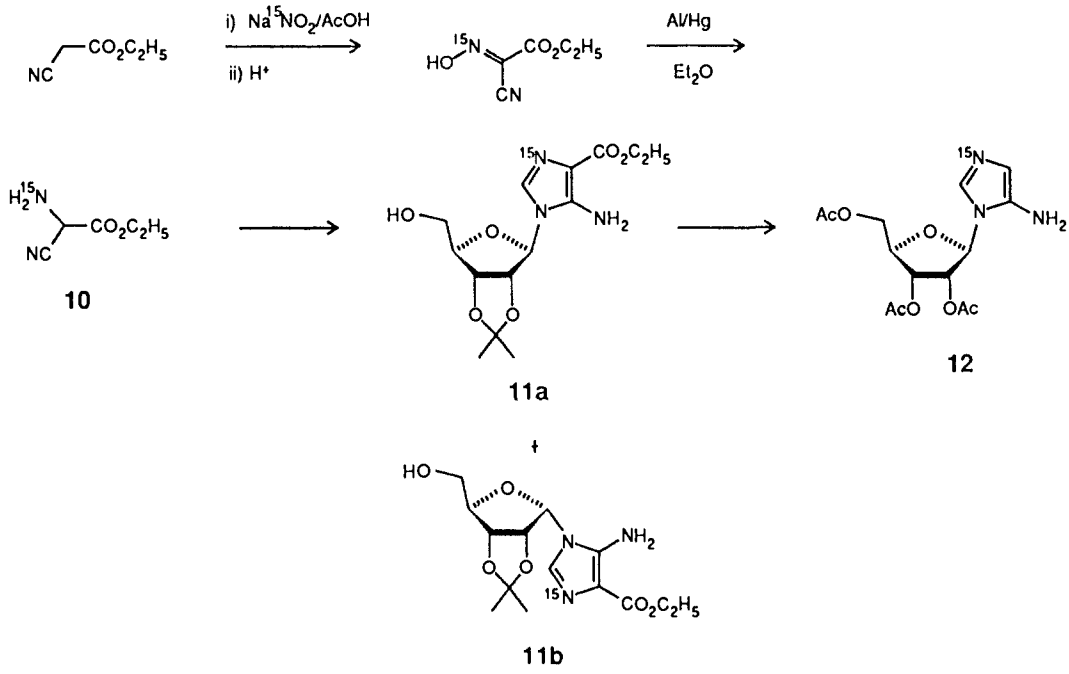
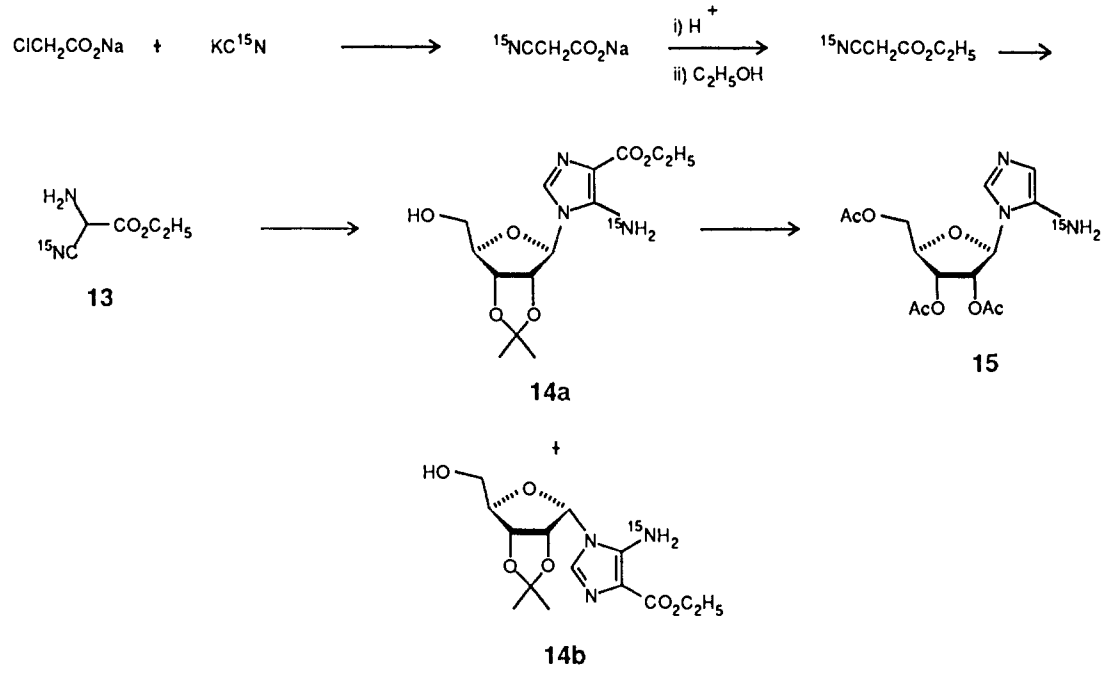
(21) Bergmann, M.; Miekeley, A. *Z. Physiol. Chem.* **1924**, *140*, 128.

Scheme II



Scheme III



modifications have been noted in the Experimental Section, along with identifying spectroscopic characteristics that were not provided previously. We performed the sequence first with unlabeled compounds. For the [1-^{15}N]-labeled series (Scheme I), crystalline [^{15}N]-2,3-*O*-isopropylidene-β-D-ribofuranosylamine *p*-toluenesulfonate (**4**) was obtained following the condensation of ribose with [^{15}N]-ammonia in methanol and further reaction with acetone, 2,2-dimethoxypropane, and *p*-toluenesulfonic acid monohydrate.[24] Compound **4** was condensed with the product of the reaction of ethyl α-amino-α-cyanoacetate[26] with triethyl orthoformate[24,25] to give a mixture (2:1) of ethyl [1-^{15}N]-5-amino-1-(2,3-*O*-isopropylidene-β- and -α-D-ribofuranosyl)imidazole-4-carboxylates (**5a,b**). The anomeric configurational assignments were based on examination of the Δδ chemical shift differences between the ^{1}H NMR signals of the isopropylidene methyl groups[27] for $(CD_3)_2SO$ solutions (see Supplementary Material) as well as for $CDCl_3$ solutions. The β isomer was deblocked in acetic acid, and the resulting ester **6** was saponified[24] to the sodium salt **7**. Treatment with acetic anhydride in pyridine at 0–10 °C[15] yielded [1-^{15}N]-5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid (**8**). This was converted to [1-^{15}N]-5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-imidazole (**9**) by the method described earlier.[14a]

For the [3-^{15}N]-labeled series (Scheme II), the requisite ethyl [α-^{15}N]-amino-α-cyanoacetate (**10**) was prepared by nitrosation

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(26) Robinson, D. H.; Shaw, G. *J. Chem. Soc. C* **1972**, 1715.
(27) (a) Chavis, C.; de Gourcy, C.; Dumont, F.; Imbach, J.-L. *Carbohydrate Res.* **1983**, *113*, 1. (b) Imbach, J.-L.; Barascut, J.-L.; Kam, B. L.; Rayner, B.; Tamby, C.; Tapiero, C. *J. Heterocycl. Chem.* **1973**, *10*, 1069.

Table I. Selected J_{NH} and J_{NC} Averaged Coupling Constants as Determined from ^{15}N Compounds Labeled Separately at N1, N3, and $\alpha(NH_2)$ Positions[a]

	14a	14b	2	3a	3b
$^2J_{NH}$ (N1/H2)	0.0	0.0	7.8	7.4	7.2
$^3J_{NH}$ (N1/H4)			3.6	2.7	2.7
$^2J_{NH}$ (N3/H2)	11.1	11.8	10.8	10.5	10.7
$^2J_{NH}$ (N3/H4)			9.0	9.1	9.3
$^1J_{NH}$ (NH/NH)	85.3	83.7	65.5	93.3	93.0
$^1J_{NC}$ (N1/C2)	9.5	9.6	n.o.	11.4	10.8
$^2J_{NC}$ (N1/C4)	7.6	7.5	8.4	8.0	7.9
$^1J_{NC}$ (N1/C5)	18.1	18.4	11.2	17.7	17.7
$^1J_{NC}$ (N1/C1')	n.o.	11.9	12.8	12.0	10.2
$^1J_{NC}$ (NH/C5)	n.o.	n.o.	n.o.	20.4	21.8

[a] In Hz (n.o. = not observed).

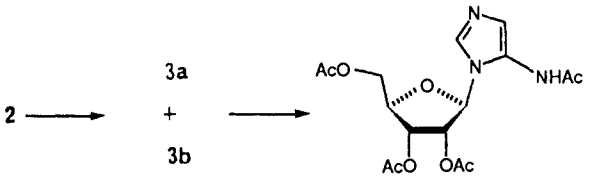
of ethyl α-cyanoacetate using $Na^{15}NO_2$, followed by reduction of the intermediate ethyl [α-^{15}N](hydroxyimino)-α-cyanoacetate[28] with aluminum amalgam in ether. The rest of the synthesis proceeded as outlined in Scheme I and led to a mixture of ethyl [3-^{15}N]-5-amino-1-(2,3-*O*-isopropylidine-β- and -α-D-ribofuranosyl)imidazole-4-carboxylates (**11a,b**). The β isomer **11a** was converted satisfactorily to [3-^{15}N]-5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (**12**).

For the [α-^{15}N]-labeled compounds (Scheme III), the series started with the synthesis[29] of ethyl [^{15}N]cyanoacetate from $KC^{15}N$ and sodium chloroacetate via sodium [^{15}N]cyanoacetate. The derived α-amino-[α-^{15}N]cyanoacetate (**13**) was converted to a mixture of ethyl [5-^{15}N]-5-amino-1-(2,3-*O*-isopropylidine-β- and -α-D-ribofuranosyl)imidazole-4-carboxylates (**14a,b**), the former of which yielded [5-^{15}N]amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (**15**) by the sequence described above.

For the previously postulated rearrangement[14a] of 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole to *N*-(imidazol-4-yl)-2,3,5-tri-*O*-acetyl-β- and -α-D-ribofuranosyl)amines in aqueous solution at neutral pH, the [1-^{15}N]- and [α-^{15}N]-labeled compounds (**9** and **15**) could be used to distinguish between migration (deribosidation, reribosidation, N1 to α-NH_2) and a Dimroth-type rearrangement (the triacetyl ribosyl unit would remain attached to the same N) (see Table I). For rearrangement via migration, the product from **9** would show $^{15}N(C2)^1H$ NMR coupling and that from **15** would show α-$^{15}N^1H$ coupling. For a Dimroth rearrangement, the product from **9** would exhibit α-$^{15}N^1H$ coupling and that from **15** would exhibit $^{15}N(C2)^1H$ coupling. Neither pattern was followed, which indicated that we had been incorrect in our original structure assignment. The most prominent feature in a comparison of the ^{15}N NMR spectra of the starting material and the rearranged product mixture was the downfield shift of about 85 ppm for the α-N of **15** in going to product. This shift could only be accommodated by the presence of an acetyl group on the α-N in the product. In addition, the $^{15}N^1H$ coupling constant, *J*, for **15** was 65.5 Hz, whereas the *J* values for the product mixture were 93.3 and 93.0 Hz. Ammonia in methanol and KCN in methanol[30] removed only two (by FAB mass spectrometry) of the three acetyl groups present in the rearranged product from **2**, which provided chemical evidence for an $NHCOCH_3$ moiety. Finally, the FTIR spectrum of the product showed a new carbonyl frequency at 1695 cm^{-1} indicative of $NHCOCH_3$, along with ester carbonyl absorption (1745 cm^{-1}) like that present initially in **2** (1750 cm^{-1}).

Which *O*-acetyl group or groups had been lost from **2** in rearrangement? It was not the 5'-*O*-acetyl group since the NMR chemical shifts for ^{1}H5' and for ^{13}C5' were not displaced appreciably in going from **2** to the rearranged product (see Experimental Section). By contrast, the chemical shifts for H2' and H3' were displaced upfield, indicative of a conversion of *H*CO-$COCH_3$ to *H*COH.[31] It was possible to assign structure **3a** to the major component since its H3' NMR signal was at lower field than that of the minor component and **3b** to the minor component since its H2' signal was at lower field than that of the major component. Displacements of ^{13}C resonances consistent with the comparison of the $HCOCOCH_3$ moiety with that of HCOH[31] supported the conclusions of the ^{1}H NMR results. The complete NMR assignments were facilitated by ^{1}H-^{13}C heteronuclear shift correlations. The assignment of the structure 5-acetamido-1-(3,5-di-*O*-acetyl-β-D-ribofuranosyl)imidazole (**3a**) to the major component of the mixture of **3a** and **3b** is consistent with the generality that, upon equilibration, acyl groups attached to glycosides tend to migrate away from the glycosidic link.[32,33]

When the mixture of **3a** and **3b** was treated with acetic anhydride and pyridine in anhydrous CH_2Cl_2 at 0 °C, a single, fully acetylated product was obtained, 5-acetamido-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (**16**), characterized by a broad



16

array of spectroscopic data. This included the low-resolution FAB mass spectrum of **16**, which showed, in addition to the *m/z* value for MH^+, a peak at 259.2 amu, ascribable to a 2,3,5-tri-*O*-acetylribosyl radical cation. The absence of a peak at *m/z* 259 for the rearranged product from **2** had been noted previously.[14a] A peak now observed at *m/z* 217.1 for the product mixture corresponds to fragmentation that produces a di-*O*-acetylribosyl radical cation, consistent with the structures **3a** + **3b**.[34]

The H4 of **2**, identified by an NMR chemical shift of 6.43 ppm in $CDCl_3$, 6.34 in ^2H_2O,[14a] was observed to exchange slowly with the deuterium of D_2O at ambient temperature. When the enamine moiety of **2** was N-acetylated, as in **16** and in **3a** + **3b**, H4 appeared at about 6.9 ppm. The deshielding effect was linked to the observation that exchange of H4 with deuterium did not occur in these derivatives.

^{15}N-Labeling at the imidazole 1, 3, and α(NH_2) locations throughout the series allowed us to assign the site of protonation at each stage. The ^{15}N NMR chemical shift data are to be found in the Experimental Section under the appropriate rubric for the unlabeled compound. In the case of ethyl 5-amino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxylate, for example, represented by **11a**, **5a**, and **14a**, the listed values of −136.6 (lowest field), −214.9, and −332.5 (t) were obtained for the [3-^{15}N]-, [1-^{15}N]-, and [α-^{15}N]-isomers. After the incremental addition of over 1 equiv of *p*-toluenesulfonic acid, the N3 resonance showed a maximal upfield movement of 78.9 ppm, whereas those of N1 and the α-N showed maximal downfield movements of 4.3 and 4.4 ppm, respectively. These observations established that this compound (represented by **11a**, **5a**, and **14a**) is monobasic and that the single protonation site is the imine N3. This general ^{15}N NMR methodology has been used to determine the preferred sites of protonation of adenine, adenosine, and their derivatives.[35] On protonation of tri-*O*-acetyl AIRs (**2**), represented by **12**, **9**, and **15**, the ^{15}N resonance of N3 showed a maximal upfield

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(30) Herzig, J.; Nudelman, A.; Gottlieb, H. E.; Fischer, B. *J. Org. Chem.* **1986**, *51*, 727.
(31) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; John Wiley and Sons: New York, NY, 1981; pp 220, 268, 271.
(32) Sugihara, J. M. *Adv. Carbohydr. Chem.* **1953**, *8*, 1.
(33) Johnston, G. A. R. *Tetrahedron* **1968**, *24*, 6987.
(34) The structures of the *N*-(imidazol-4-yl)-2,3,5-tri-*O*-acetyl-α- and -β-D-ribofuranosylamines (**6a**) on page 7175 in ref 14a should be corrected. The rearrangement product is now established to be a mixture of **3a** and **3b** (formula numbers this article).
(35) Gonnella, N. C.; Nakinishi, H.; Holtwick, J. B.; Horowitz, D. S.; Kanamori, K.; Leonard, N. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2050.

movement of 91.0 ppm, whereas those of N1 and the α-N showed maximal downfield movements of 6.4 and 8.9 ppm, respectively. Thus, 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (tri-*O*-acetyl AIRs) is monobasic, with a single protonation site at the imine N3. Titration of AIRs (**1a**) gave a single pK_a value of 6.05 in aqueous solution, consistent with protonation at N3. The site of protonation was further confirmed by observation of the ^1H and ^{13}C chemical shift differences brought about by the addition of 1 mol equiv of methanesulfonic acid to AIRs. Inter alia, the signals for H2 and C2 showed the greatest downfield shifts, corresponding to the deshielding effect of protonation of the ring imine moiety.

In deuteriochloroform solution, the ^{15}N resonances of 5-amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic acid (tri-*O*-acetyl CAIRs, e.g., **8**) for N3, N1, and α(NH_2) were very close to the corresponding values of the ethyl ester. This comparison leads us to conclude that the carboxylic acid is not in the zwitterionic form in the organic solvent. Titration of CAIRs sodium salt, sodium 5-amino-1-(β-D-ribofuranosyl)-imidazole-4-carboxylate (**7**, without label) at 27 °C in aqueous solution gave pK_a values of 2.9 and 5.9 (lit.[36] 3.00 and 6.34), assignable to COOH deprotonation and $N3^+$–H deprotonation, respectively. We suggest that CAIRs is zwitterionic in aqueous solution at pH values near 4.5 and this has mechanistic implications for the *decarboxylation* process that we have employed successfully (pH 4.8) for the chemical synthesis of AIRs. It remains to be determined whether the enzymatic process for the *carboxylation*[37] of AIR involves a zwitterionic intermediate at this stage in the biosynthesis of purine ribonucleotides.

Experimental Section

General Methods. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 7199 Fourier transform spectrophotometer. Ultraviolet spectra were recorded on a Beckman Acta MVI spectrophotometer. Titration data were obtained by using a Brinkmann Instruments pH meter 101 and Acculute titrants. Low- and high-resolution fast atom bombardment (FAB) mass spectra were obtained in the Mass Spectrometry Laboratory, School of Chemical Sciences (GM 27029). Radial preparative-layer chromatography was performed on a Chromatotron instrument (Harrison Research, Inc., Palo Alto, CA), by using Merck silica gel-60 with fluorescent indicator as the adsorbent.

Pyridine and acetonitrile were dried by distillation from CaH_2 under nitrogen; the pyridine was stored over KOH. Dichloromethane was dried by distillation from P_2O_5 under nitrogen. 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxamide (AICA riboside) was purchased from the Sigma Chemical Co., St. Louis, MO. 99% [^{15}N]Ammonia gas was purchased from the Aldrich Chemical Co., Milwaukee, WI. 99% [^{15}N]KCN was obtained from ICON Services, Inc., and 99% [^{15}N]$NaNO_2$ was from Stohler Isotope Chemicals.

NMR Methods. ^1H and ^{13}C NMR spectra were recorded for deuteriochloroform or deuterium oxide solutions and were obtained on either a Varian XL-200 (200 and 50 MHz), General Electric QE-300 (300 and 75.5 MHz), Nicolet NT-360 (360 and 90 MHz), or the GN-500 (500, 125 MHz) instrument. These spectra were referenced to internal tetramethylsilane ($Si(CH_3)_4$) or sodium 3-(trimethylsilyl)-1-propanesulfonate (D_2O) set to 0.0 ppm for ^1H NMR spectra or to chloroform (77.0 ppm for $CDCl_3$) or dioxane (66.0 ppm for D_2O) for ^{13}C NMR spectra. Peak assignments were made with the assistance of both short- and long-range 2D ^1H–^{13}C heteronuclear correlation spectroscopy (Hetcor), obtained on the QE-300 instrument. ^1H and ^{13}C NMR spectral data recorded for $(CD_3)_2SO$ solutions are included as Supplementary Material.

The ^{15}N NMR spectra were recorded for deuteriochloroform solutions on a General Electric GN-500 spectrometer operating at 50.864 MHz, with [^{15}N]CH_3NO_2 (0.0 ppm) as the external reference. The machine drift during ^{15}N NMR spectra acquisition was determined to be less than 0.5 ppm. The ^{15}N NMR spectral data descriptions are based upon the combined data obtained for the 1-[^{15}N]-, 3-[^{15}N]-, and α-[^{15}N]-labeled versions of the compounds.

5-Amino-1-(β-D-ribofuranosyl)imidazole (AIRs, 1a). A solution of **7** (without label) (1.34 g, 4.8 mmol) in 0.25 M aqueous NaOAc/AcOH buffer (pH 4.8, 50 mL) was maintained at 27 °C for 24 h with N_2 bubbling through and was then loaded onto a Dowex-50W-X8 column (NH_4^+ form). The column was washed with 500 mL of water to remove salts and then eluted with 500 mL of 1.0 N NH_4OH. The basic eluate was lyophilized. The residue was dissolved in water (25 mL) and relyophylized to afford 861 mg (88%) of **1a** (AIRs) as a pale grey hygroscopic solid: mp 92–94 °C; ^1H NMR (D_2O) δ 7.52 (s, 1, H2), 6.34 (s, exchanges slowly, 1, H4), 5.57 (d, J = 6.0 Hz, 1, H1′), 4.43 (pseudo-t, 1, H2′), 4.21 (pseudo-t, 1, H3′), 4.05 (m, 1, H4′), 3.69 (m, 2, 5′CH_2); ^{13}C NMR (D_2O) δ 135.4 (C5), 131.0 (C2), 112.1 (C4), 86.8 (C1′), 84.3 (C4′), 73.1 (C3′), 69.7 (C2′), 60.7 (C5′). The addition of 1 mol equiv of methanesulfonic acid revealed ^1H NMR chemical shifts of 8.38, 6.69, and 5.65 ppm for H2, H4, and H1′, respectively, and ^{13}C NMR chemical shifts of 137.4, 128.0, 102.5, and 89.2 ppm for C2, C5, C4, and C1′, respectively: low-resolution FAB mass spectrum, m/z 216.1 (MH^+); high-resolution FAB mass spectrum, m/z 216.0977 obsd ($C_8H_{14}N_3O_4$ requires 216.0984); UV λ_{max} nm (ε × 10^3) (pH 1) 210 (4.6), (pH 7) 214 (4.5), (pH 11) 234 (3.7). Titration at 27 °C revealed one pK_a at 6.05, assigned to the imine N3.

5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (Tri-*O*-acetyl AIRs, without Label (2), Also 9, 12, and 15). A solution of **8** (as representative) (0.2 g, 0.52 mmol) in 0.25 M aqueous NaOAc/AcOH buffer was allowed to stand for 1.5 h at 35–40 °C under N_2. The product was extracted into $CHCl_3$ and purified by chromatography on Florisil (15% MeOH/$CHCl_3$ as eluent) to afford **2** as a foam-powder in 65% yield: ^1H NMR ($CDCl_3$) δ 7.34 (s, 1, H2), 6.43 (s, exchanges slowly, 1, H4), 5.77 (d, J = 5.4 Hz, 1, H1′), 5.64 (m, 1, H2′), 5.41 (m, 1, H3′), 4.36 (m, 3, H4′ and 5′CH_2), 2.13–2.10 (m, 9, three CH_3CO_2); ^{13}C NMR ($CDCl_3$) δ 170.2–169.4 (three CH_3CO), 134.9 (C2), 130.9 (C5), 114.9 (C4), 86.1 (C1′), 79.5 (C4′), 72.3 (C2′), 69.6 (C3′), 62.4 (C5′), 20.3–20.2 (three CH_3CO_2); ^{15}N NMR δ −128.3 (N3), −212.8 (N1), −354.5 (t, $^1J_{NH}$ = 65.5 Hz, NH_2). After the incremental addition of over 1 mol equiv of methanesulfonic acid, the ^{15}N resonance of N3 showed a maximal upfield movement of 91.0 ppm, whereas that of N1 and NH_2 showed maximal downfield movements of 6.4 and 8.9 ppm, respectively. Thus, **2** is monobasic, with a single protonation site at the imine N3: FTIR ($CHCl_3$) 1750 cm^{-1} (C=O); low-resolution FAB mass spectrum, m/z 342.3 (MH^+), 259.2 (2,3,5-tri-*O*-acetylribosyl radical cation); high-resolution FAB mass spectrum, m/z 342.1299 obsd ($C_{14}H_{20}N_3O_7$ requires 342.1301); UV λ_{max} nm (ε × 10^3) (pH 1) 210 (3.7), (pH 7) 213 (4.4), (pH 11) 236 (3.5).

5-Amino-1-(β-D-ribofuranosyl)imidazole 5′-Phosphate (AIR, 1). A suspension of **1a** (0.20 g, 0.39 mmol) in 5 mL of anhydrous *m*-cresol was cooled to 0 °C under Ar and was treated with pyrophosphoryl chloride (0.37 g, 1.46 mmol). The mixture was stirred at 0–2 °C for 4.25 h, after which time the starting material had dissolved. The mixture was then poured into 50 mL of an ice–water mixture and was extracted with diethyl ether (3 × 100 mL) to remove the *m*-cresol. The aqueous layer was immediately adjusted to pH 7.4 by the dropwise addition of 1 N NaOH, was rotary evaporated in vacuo for 0.5 h to remove traces of diethyl ether, and was diluted to 500 mL with distilled water. This solution was loaded onto a column of Sephadex A-25 anion exchange resin (already equilibrated with 0.1 M, pH 7.4 aqueous triethylammonium bicarbonate (TEAB) buffer). The column was washed with distilled water (200 mL) and then was eluted with a linear gradient of 0–400 mM pH 7.4 aqueous TEAB buffer. Appropriate fractions (UV analysis) were pooled and lyophilized. Excess TEAB was removed by repeated coevaporation with 1:1 MeOH/H_2O. The resulting gum was dried in vacuo for several hours at room temperature to afford a greater-than-theoretical amount of AIR, monotriethylammonium salt (**1**-Et_3NH^+) contaminated only with TEAB (by ^1H NMR), as a hygroscopic gum: ^1H NMR (D_2O) δ 8.59 (s, 1, H2), 6.78 (s, 1, H4), 5.89 (d, J = 4.8 Hz, 1, H1′), 4.58 (m, 1, H2′), 4.43 (m, 1, H3′), 4.37 (m, 1, H4′), 4.14 (m, 2, 5′CH_2); low-resolution FAB mass spectrum, m/z 296.1 (MH^+).

Monoammonium Salt (1-NH_4^+). A solution of **1**-Et_3NH^+ in 100 mL of distilled water was loaded onto a column of Dowex-50X-W8 (NH_4^+ form) cation exchange resin. The column was washed with water and then was eluted with 20 mM aqueous NH_4OH. The aqueous NH_4OH washing was rotary evaporated, and the residue was dried in vacuo to afford 204 mg (70%) of AIR-monoammonium salt (**1**-NH_4^+), as a thick hygroscopic gum: ^1H NMR (D_2O) δ 8.57 (s, 1, H2), 6.70 (s, exchanges with a half-life of about 2 min, 1, H4), 5.85 (d, J = 5.1 Hz, 1, H1′), 4.61 (m, 1, H2′), 4.45 (m, 1, H3′), 4.34 (m, 1, H4′), 4.04 (m, 2, 5′CH_2); ^{13}C NMR (D_2O) δ 136.4 (C5), 127.9 (C2), 102.6 (C4), 88.5 (C1′), 84.0 (d, $^3J_{CP}$ = 8.4 Hz, C4′), 74.0 (C2′), 69.1 (C3′), 62.8 (d, $^2J_{CP}$ = 3.2 Hz, C5′); low-resolution FAB mass spectrum, m/z 296.1 (MH^+); high-resolution FAB mass spectrum, m/z 296.0653 obsd ($C_8H_{15}N_3PO_7$ requires 296.0648).

Monolithium Salt (1-Li^+). A solution of **1**-NH_4^+ in 20 mL of water was loaded onto a column of Dowex-50X-W8 (Li^+ form) cation exchange resin. The column was eluted with water, and the combined appropriate

(36) Litchfield, G. J.; Shaw, G. *J. Chem. Soc. C* **1971**, 817.
(37) For chemical carboxylation of AIR, see: Alenin, V. V.; Kostikova, T. R.; Domkin, V. D. *Zh. Obshch. Khim.* **1987**, *57*, 692.

fractions (UV analysis) were rotary evaporated in vacuo. The residue was treated with a small amount of CH_3OH, and the resulting solid was collected by suction filtration, washed with CH_3OH (3 × 5 mL), washed with Et_2O (3 × 5 mL), and dried in vacuo to afford 180 mg (90%) of AIR-monolithium salt (**1**-Li^+), as a colorless hygroscopic solid: ^1H NMR (D_2O) δ 8.55 (s, 1, H2), 6.70 (s, exchanges with a half life of about 2 min, 1, H4), 5.85 (d, J = 5.1 Hz, 1, H1′), 4.62 (m, 1, H2′), 4.45 (m, 1, H3′), 4.34 (m, 1, H4′), 4.10 (m, 2, 5′CH_2); ^{13}C NMR (D_2O) δ 136.3 (C5), 128.2 (C2), 103.5 (C4), 88.3 (C1′), 84.0 (d, $^3J_{CP}$ = 9.1 Hz, C4′), 74.0 (C2′), 69.2 (C3′), 62.7 (d, $^2J_{CP}$ = 3.2 Hz, C5′).

[^{15}N]-2,3-*O*-Isopropylidine-β-D-ribofuranosylamine *p*-Toluenesulfonate (4). This compound was prepared by substituting 99.0% [^{15}N]NH_3 for NH_3 in a literature procedure.[24] After drying in vacuo, the white crystalline product had mp 135–136 °C (lit.[24] 128–129 °C), identical with that of the freshly prepared unlabeled product: low-resolution FAB mass spectrum, m/z 381.3 ($MH^+ + H_2O$), 363.2 (MH^+), 191.2 ($MH^+ - C_7H_7SO_3$), 173.2 (2,3-*O*-isopropylidine-D-ribofuranosyl radical cation).

Ethyl α-(Hydroxyimino)-α-cyanoacetate. This compound was prepared from ethyl cyanoacetate and $NaNO_2$ (or $Na^{15}NO_2$) in glacial acetic acid according to the literature procedure[28] in a 68% yield.

Ethyl α-Amino-α-cyanoacetate (without Label, Also 10 and 13). This compound was prepared according to the literature procedure[9] and was purified by flash chromatography (2% MeOH/$CHCl_3$ on silica gel) to give the product in 50% yield as a pale yellow oil, homogeneous by TLC analysis. The use of 99% [^{15}N]$NaNO_2$ or 99% [^{15}N]KCN in this procedure afforded the precursors to the 3-[^{15}N]- or α-[^{15}N]-labeled series of products, respectively.

Ethyl 5-Amino-1-(2,3-*O*-isopropylidine-β-D-ribofuranosyl)imidazole-4-carboxylate (without Label, Also 5a, 11a, and 14a). The literature procedure[24,25] was employed to prepare this material; however, in our hands the α:β ratio obtained was 1:2, not 3:2: ^1H NMR ($CDCl_3$) δ 7.26 (s, 1, H2), 7.12 (s, exchanges, 1, OH), 5.64 (br s, exchanges, 2, NH_2), 5.61 (d, J = 3.0 Hz, 1, H1′), 5.02 (m, 2, H2′ and H3′), 4.33 (m, 3, H4′ and 5′CH_2), 3.95 (q, 2, CH_2CH$_3$), 1.62 and 1.38 (each s, each 3, C-(CH_3)$_2$), 1.36 (t, 3, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$) δ 164.4 (C=O), 145.4 (C5), 130.2 (C2), 114.5 (*C*(CH_3)$_2$), 111.4 (C4), 93.0 (C1′), 85.1 (C4′), 82.3 (C2′), 82.3 (C3′), 61.3 (C5′), 59.7 (CO_2CH_2), 27.2 and 25.1 (C-(*C*H$_3$)$_2$), 14.5 (CH_2CH_3); ^{15}N NMR δ −136.6 (N3), −214.9 (N1), −332.5 (t, $^1J_{NH}$ = 85.3 Hz, NH_2). After the incremental addition of over 1 equiv of *p*-toluenesulfonic acid, the ^{15}N resonance of N3 showed a maximal upfield movement of 78.9 ppm, whereas those of N1 and NH_2 showed maximal downfield movements of 4.3 and 4.4 ppm, respectively. Thus, the compound is monobasic and has a single protonation site at the imine N3: low-resolution FAB mass spectrum, m/z 328.2 (MH^+), 173.2 (2,3-*O*-isopropylidine-D-ribofuranosyl radical cation), 156.2 (BH^+).

5a: low-resolution FAB mass spectrum, m/z 329.3 (MH^+), 173.1 (2,3-*O*-isopropylidine-D-ribofuranosyl radical cation), 157.1 (BH^+).

11a: low-resolution FAB mass spectrum, m/z 329.2 (MH^+), 173.2 (2,3-*O*-isopropylidine-D-ribofuranosyl radical cation), 157.2 (BH^+).

14a: low-resolution FAB mass spectrum, m/z 329.2 (MH^+), 173.2 (2,3-*O*-isopropylidine-D-ribofuranosyl radical cation), 157.2 (BH^+).

Ethyl 5-Amino-1-(2,3-*O*-isopropylidine-α-D-ribofuranosyl)imidazole-4-carboxylate (without Label, Also 5b, 11b, and 14b). Formed along with the β-anomer: ^1H NMR ($CDCl_3$) δ 7.28 (s, 1, H2), 5.89 (d, J = 2.4 Hz, 1, H1′), 5.05 (br s, exchanges, 2, NH_2), 4.94 (m, 1, H2′), 4.49 (m, 2, H3′ and H4′), 4.36 (m, 2, 5′CH_2), 3.89 (q, 2, CH_2CH$_3$), 1.41 (t, 3, CH$_2$CH_3), 1.37 and 1.31 (each s, each 3, C(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ 164.5 (C=O), 144.9 (C5), 130.6 (C2), 113.6 (*C*(CH_3)$_2$), 111.0 (C4), 87.1 (C1′), 83.7 (C4′), 82.1 (C2′), 80.2 (C3′), 63.6 (C5′), 59.8 (CO_2CH_2), 25.4 and 24.2 (C(*C*H$_3$)$_2$), 14.5 (CH_2CH_3); ^{15}N NMR δ −136.8 (N3), −216.1 (N1), −334.8 (t, $^1J_{NH}$ = 83.7 Hz, NH_2); low-resolution FAB mass spectrum, m/z 328.3 (MH^+), 173.3 (2,3-*O*-isopropylidine-D-ribofuranosyl radical cation), 156.2 (BH^+).

Ethyl 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (without Label, Also 6). The yields obtained in the removal of the 2,3-*O*-isopropylidine moiety were consistently lower than those reported previously.[24] We believe this to be due to decomposition of product in the 100 °C aqueous HOAc: low-resolution FAB mass spectrum, m/z 288.2 (MH^+), 155.1, also 156 (BH^+).

Sodium 5-Amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (CAIRs Sodium Salt, without Label, Also 7). This compound was prepared from AICA riboside according to the literature procedure, reproducibly in 55–66% yields.[15] The substitution of 0.5 N NaOH for 6 N NaOH was used when the starting material was the 4-ethoxycarbonyl derivative: ^1H NMR (D_2O) δ 7.41 (s, 1, H2), 5.58 (d, J = 5.7 Hz, 1, H1′), 4.55 (m, 1, H2′), 4.26 (m, 1, H3′), 4.14 (m, 1, H4′), 3.80 (m, 2, 5′CH_2); ^{13}C NMR (D_2O) δ 172.1 (CO_2Na), 142.4 (C5), 129.7 (C2), 116.7 (C4), 87.9 (C1′), 85.5 (C4′), 73.3 (C2′), 70.4 (C3′), 61.2 (C5′); FTIR (KBr) 3400–3200 (OH), 2930, 1617 (C=O), 1586, 1530 (sh), 1505, 1461, 1410, 1335 (sh), 1301, 1260, 1206, 1178, 1130–1030 cm^{-1}. Titration at 27 °C revealed pK_{a_1} = 2.9 and pK_{a_2} = 5.9 (lit.[36] 3.00 and 6.34), assignable to COOH deprotonation and N3$^+$–H deprotonation, respectively.

5-Amino-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylic Acid (Tri-*O*-acetyl CAIRs, without Label, Also 8): mp 135–140 °C (loses CO_2, lit.[15] 145–146 °C); ^1H NMR ($CDCl_3$) δ 7.35 (s, 1, H2), 5.70 (d, J = 4.4 Hz, 1, H1′), 5.68 (s, exchanges with D_2O, 2, NH_2), 5.44 (m, 1, H2′), 5.30 (m, 1, H3′), 4.45 (m, 1, H4′), 4.42 (m, 2, 5′CH_2), 2.18–2.15 (m, 9, three CH_3CO_2); ^{13}C NMR ($CDCl_3$) δ 170.0–169.5 (three CH_3CO), 166.2 (CO_2H), 145.0 (C5), 128.7 (C2), 112.0 (C4), 87.0 (C1′), 80.2 (C4′), 72.7 (C2′), 69.2 (C3′), 62.0 (C5′), 20.7–20.4 (three *C*H_3CO_2); ^{15}N NMR δ −135.4 (N3), −217.4 (N1), −333.8 (t, $^1J_{NH}$ = 85.6 Hz, NH_2); low-resolution FAB mass spectrum, m/z 430.1 (MNa^+ of CO_2Na form), 408.1 (MNa of CO_2H form), 386.1 (MH^+ of CO_2H form); UV λ_{max} nm (ε × 10^3) (pH 7) 248 (10.8); FTIR (KBr) 3570, 3500 (sh), 3435, 3343, 1750 (C=O), 1745 (sh) (C=O), 1685 (C=O), 1621, 1574, 1467, 1382, 1246, 1225, 1216; ($CHCl_3$) 3450, 3350, 1750 (C=O), 1685 weak (C=O), 1627 (C=O), 1560, 1407, 1376, 1242 cm^{-1}.

The decarboxylation of **8** in 0.5 M pH 7 phosphate buffer at 27 °C for 48 h afforded rearrangement product mixture **3** in a 74% yield. The thermal decarboxylation of **8** at 155–160 °C (neat, for 10 min under N_2) afforded a mixture of **2** and **3**, isolated by radial chromatography (5% MeOH/CH_2Cl_2 as eluent) in 67% and 29% yield, respectively.

2:1 Mixture of 5-Acetamido-1-(3,5-di-*O*-acetyl-β-D-ribofuranosyl)-imidazole (3a) and 5-Acetamido-1-(2,5-di-*O*-acetyl-β-D-ribofuranosyl)-imidazole (3b). This mixture was obtained from the decarboxylation of tri-*O*-acetyl CAIRs at pH 7 (see above) or from the rearrangement of authentic tri-*O*-acetyl AIRs at pH 7: ^1H NMR ($CDCl_3$) δ 9.23 (s, exchanges, 1, **3a**-NH), 9.16 (s, exchanges, 1, **3b**-NH), 7.79 (s, exchanges, 1, **3b**-OH), 7.65 (s, exchanges, 1, **3a**-OH), 7.61 (s, 1, **3b**-H2), 7.54 (s, 1, **3a**-H2), 6.95 (s, 1, **3b**-H4), 6.85 (s, 1, **3a**-H4), 5.68 (d, J = 1.5 Hz, **3b**-H1′), 5.53 (d, J = 5.5 Hz, **3a**-H1′), 5.31 (m, 1, **3b**-H2′), 5.11 (m, 1, **3a**-H2′), 4.47 (m, 1, **3a**-H3′), 4.31 (m, 7, **3b**-H3′, **3b**-H4′, **3a**-H4′, **3a**-5′CH_2, and **3b**-5′CH_2), 2.12–2.05 (m, 6, four CH_3CO_2 and two CH_3CONH); ^{13}C NMR ($CDCl_3$) δ 175.0 (**3a**-CH_3*C*ONH), 171.3–169.8 (four CH_3CO_2 and **3b**-CH_3*C*ONH), 132.2 (**3a**-C2), 131.4 (**3b**-C2), 126.1 (**3a**-C5), 125.8 (**3b**-C5), 122.7 (**3a**-C4), 120.9 (**3b**-C4), 88.6 (**3a**-C1′), 86.9 (**3b**-C1′), 80.7 (**3b**-C4′), 80.0 (**3a**-C4′), 77.6 (**3b**-C2′), 73.5 (**3a**-C3′), 72.1 (**3a**-C2′), 67.6 (**3b**-C3′), 63.1 (**3a**-C5′), 62.5 (**3b**-C5′), 22.7 (**3a**-*C*H_3CONH and **3b**-*C*H_3CONH), 20.6 (four *C*H_3CO_2); ^{15}N NMR δ −133.0 (**3a**-N3), −133.3 (**3b**-N3), −207.1 (**3b**-N1), −207.2 (**3a**-N1), −269.0 (d, $^1J_{NH}$ = 93.0 Hz, **3b**-NH), −269.9 (d, $^1J_{NH}$ = 93.3 Hz, **3a**-NH); FTIR ($CHCl_3$) 1745 (C=O), 1695 cm^{-1} (C=O); low-resolution FAB mass spectrum, m/z 342.2 (MH^+), 217.1 (di-*O*-acetylribosyl radical cation); high-resolution FAB mass spectrum, m/z 342.1293 obsd ($C_{14}H_{20}N_3O_7$ requires 342.1301); UV λ_{max} nm (ε × 10^3) (pH 1) 212 (5.0), (pH 7) 214 (5.5), (pH 11) 255 (3.3).

5-Acetamido-1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)imidazole (16). A solution of **3** (mixture) (100 mg, 0.29 mmol) in 4.0 mL of anhydrous CH_2Cl_2 at 0 °C under nitrogen was treated with 53 μL (0.65 mmol) of anhydrous pyridine and 57 μL (0.60 mmol) of acetic anhydride. The mixture was stirred at 0 °C for 4 h and rotary evaporated at room temperature, and the product was purified by radial chromatography (10% MeOH/CH_2Cl_2) to afford 97 mg (86%) of **16** as a yellow foam. The compound was identical (in TLC R_f value and ^1H NMR spectral properties) to one obtained by acetylation of the crude product mixture of the preparation of tri-*O*-acetyl CAIRs: ^1H NMR ($CDCl_3$) δ 9.52 (s, exchanges, 1, NH), 7.01 (s, 1, H2), 6.96 (s, 1, H4), 5.77 (d, J = 3.2 Hz, 1, H1′), 5.50 (m, 1, H2′), 5.33 (m, 1, H3′), 4.34 (m, 3, H4′ and 5′CH_2), 2.14 (s, 3, NHCOCH_3), 2.11–2.00 (m, 9, three CH_3CO_2); ^{13}C NMR ($CDCl_3$) δ 169.9–169.2 (NH*C*OCH$_3$ and three CH_3CO), 131.7 (C2), 125.7 (C5), 122.3 (C4), 86.1 (C1′), 78.8 (C4′), 73.6 (C2′), 68.9 (C3′), 61.9 (C5′), 22.3 (NHCO*C*H$_3$), 20.2–20.0 (three *C*H_3CO_2); FTIR ($CHCl_3$) 1750 (C=O), 1695 cm^{-1} (C=O); low-resolution FAB mass spectrum, m/z 384.2 (MH^+), 259.2 (2,3,5-tri-*O*-acetylribosyl radical cation).

5-Acetamido-1-(β-D-ribofuranosyl)imidazole (*N*-Acetyl AIRs). A solution of **3** (mixture) (0.10 g, 0.29 mmol) and KCN (5 mg, 0.07 mmol) in anhydrous MeOH (15 mL)[30] was stirred at room temperature for 5 h, at which time TLC (25% MeOH/$CHCl_3$) showed the reaction to be complete. Solvent was removed under reduced pressure, and the product was purified on a short silica gel column using 25–30% MeOH/$CHCl_3$ as the eluent. Appropriate fractions were combined. Addition of ether, filtration, and drying of the collected colorless solid yielded 60 mg (80%). Similar results were obtained when methanolic ammonia was used instead of KCN: ^1H NMR (D_2O) δ 7.94 (s, 1, H2), 6.98 (s, 1, H4), 5.58 (d, J = 4.8 Hz, 1, H1′), 4.45 (m, 1, H2′), 4.31 (m, 1, H3′), 4.12 (m, 1, H4′), 3.80 (m, 2, 5′CH_2), 2.20 (s, 3, $COCH_3$); ^{13}C NMR (D_2O) δ 175.3 (C=O), 135.0 (C2), 125.2 (C5), 123.5 (C4), 87.8 (C1), 84.4 (C4), 74.3 (C2), 69.7 (C3), 60.7 (C5), 21.8 (CH_3); low-resolution FAB mass

spectrum, m/z 258.1 (MH^+).

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Supplementary Material Available: ^1H and ^{13}C NMR spectral data recorded for $(CD_3)_2SO$ solutions (3 pages). Ordering information is given on any current masthead page.

Mechanism of the Asymmetric Isomerization of Allylamines to Enamines Catalyzed by 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl–Rhodium Complexes

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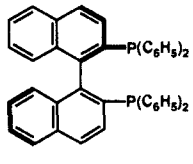
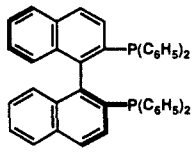
Abstract: Cationic Rh complexes containing the 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) ligand catalyze a highly enantioselective isomerization of diethylgeranylamine or -nerylamine to give (*R*)- or (*S*)-citronellal (*E*)-diethylenamine in >95% ee. A new, nitrogen-triggered mechanism is postulated for the double-bond-migration reaction on the basis of ^1H and ^{31}P NMR studies, kinetic measurements, and deuterium-labeling experiments. The initial nitrogen-coordinated allylamine–Rh^+ complex causes a four-centered hydride elimination from C(1) via dissociative mechanism to generate a transient iminium–RhH complex. Delivery of the hydrogen from Rh to C(3) gives the enamine η^3-complex. The latter, having an aza-allyl structure, serves as the chain carrier in the catalytic cycle. The BINAP–Rh^+ complexes differentiate efficiently the enantiotopic C(1) hydrogens of the allylamines through interaction with the adjacent nitrogen atoms. The overall 1,3-hydrogen shift occurs in a suprafacial manner from an s-trans-type conformer of the flexible substrates. The origin of the chiral recognition has been interpreted in terms of the chiral environments of the BINAP-based Rh^+ complexes.

The successful design of the 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) ligand (**1**),[1] characterized by C_2 chirality, a fully arylated structure, and molecular pliancy, has allowed innovative asymmetric catalyses with transition-metal complexes.[2] The cationic Rh complexes possessing this unique diphosphine ligand cause asymmetric isomerization of diethylgeranylamine (**2**) or -nerylamine to give citronellal (*E*)-diethylenamine (**3**) in >95% ee.[3] This highly enantioselective



(*R*)-1

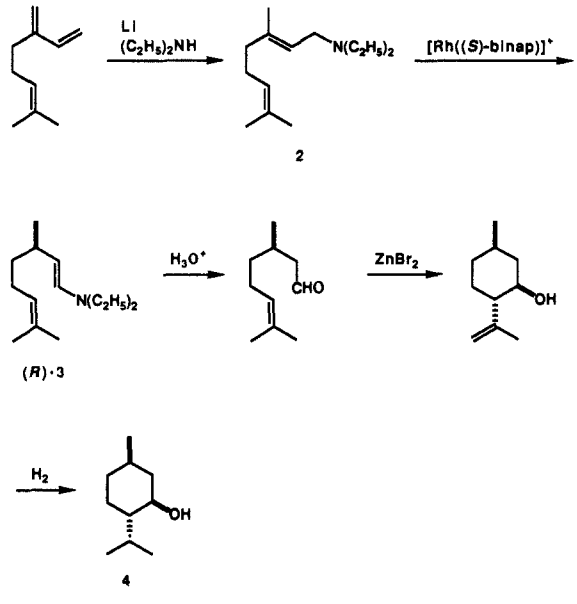


(*S*)-1

reaction now serves as a key step in the industrial production of (−)-menthol (**4**)[4] (Scheme I), providing an example of the most effective applications of transition-metal-catalyzed asymmetric reactions in homogeneous phase which have been developed during the past two decades.[5]

We describe herein the mechanism and steric course of the isomerization, elucidated by using ^1H and ^{31}P NMR techniques, kinetic study, and deuterium-labeled experiments. For transition-metal-catalyzed double bond migration, two mechanisms have been recognized.[6] One is the metal hydride addition–elimination mechanism (eq 1)[7] and the other is the π-allyl mechanism resulting

Scheme I



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